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(FILE 'HOME' ENTERED AT 15:43:25 ON 17 JAN 2006)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, LIFESCI' ENTERED AT 15:43:51 ON 17 JAN 2006

L1 251508 S RESTENOSIS OR STENOSIS
L2 14344 S ZUCKER(3A)RAT
L3 32 S L1 AND L2
L4 2636332 S PROBLEM OR DIFFICULT? OR UNPREDICT?
L5 1 S L3 AND L4
L6 18 DUP REM L3 (14 DUPLICATES REMOVED)

=> d au ti so pi ab 1-18 16

L6 ANSWER 1 OF 18 MEDLINE on STN DUPLICATE 1
AU Desouza Cyrus V; Gerety Moira; Hamel Frederick G
TI Neointimal hyperplasia and vascular endothelial growth factor expression are increased in normoglycemic, insulin resistant, obese fatty rats.
SO Atherosclerosis, (2006 Feb) 184 (2) 283-9. Electronic Publication: 2005-06-06.
Journal code: 0242543. ISSN: 0021-9150.
AB OBJECTIVE: Insulin resistance is associated with a constellation of factors that enhance the artherosclerotic process. Vessel injury results in the formation of a markedly increased neointima in type 2 diabetes. Increased neointimal hyperplasia (NH) and vascular endothelial growth factor (VEGF) expression may lead to **restenosis** post angioplasty. We studied NH and VEGF expression in an obese, insulin resistant, but normoglycemic rat model, after carotid balloon injury. METHODS AND RESULTS: Diabetic rats (ZDF, n=10), normoglycemic, insulin-resistant rats (ZDF-normoglycemic, n=6) as well as **Zucker** fatty **rats** (FZ, n=6), and lean **Zucker rats** (LZ, n=6), all 13-16 weeks old, were subjected to right carotid injury by an angioplasty catheter introduced via the femoral artery. Three weeks later the rats were sacrificed and serum and carotids obtained. The intima-media ratio (I/M) was then calculated. ZDF-normoglycemic, FZ and ZDF-diabetic rats were all hyperinsulinemic and hypertriglyceridemic when compared to LZ rats. ZDF diabetic rats were hyperglycemic while FZ, ZDF-normoglycemic and LZ rats were normoglycemic. The I/M ratio for ZDF and FZ rats were significantly greater than for LZ rats. The VEGF expression was significantly greater in ZDF and FZ rats than LZ rats. CONCLUSIONS: In conclusion, insulin resistance increases neointimal hyperplasia and VEGF expression even with normoglycemia, after carotid angioplasty in rats.

L6 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
IN Lardy, Claude; Guedat, Philippe; Caputo, Lidia
TI Preparation of nitroso derivatives of diphenylamine as antioxidants and spontaneous nitric acid donors, pharmaceutical compositions containing them, and their use in the treatment of pathologies characterized by oxidative stress
SO Fr. Demande, 63 pp.
CODEN: FRXXBL

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2862966	A1	20050603	FR 2003-13953	20031127
WO 2005051896	A1	20050609	WO 2004-EP14892	20041117

PI
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AB The invention relates to compds. I [wherein R1 = independently halo, CN, NH2, (un)substittued alkyl optionally interrupted by O or S, etc.; R2 = independently CN, OH, alkylcarbonyl, CO2H and derivs., etc.; n, m = independently 1-5; with the exception of the compds. for which i = j = 1, R1 = CO2H, R2 = alkoxycarbonyl or R1 = CF3 and R2 = CO2H; and their derivs., salts, solvates, stereoisomers and pharmaceutically acceptable salts, including their mixts. in all proportions]. I are useful in the treatment of pathologies which are characterized by a condition of oxydative stress, and a deficit of the availability of endothelial nitric oxide (NO). I are generally prepared via the corresponding diphenylamines. Thus, reacting N-(4-methoxyphenyl)formamide with Et 4-fluorobenzoate, followed by saponification of the ester (no data), and nitrosation with NaNO2 in AcOH/H2O gave II (m.p. = 169-171°). At 150 μM in a test solution, compds. I spontaneously liberated NO, giving a colorimetric nitrate-nitrite level of 38-108 μM. In an in vitro test for antioxidant effect on the cupric ion-induced oxidation of human LDL in vitro, II had an IC50 of 17.0 μM. II reduced triglycerides by 58% in **Zucker** fatty **rats** after its administration for 8 days at 200 mg/kg/day/p.o.

L6 ANSWER 3 OF 18 MEDLINE on STN DUPLICATE 2

AU Takeda Ryo; Suzuki Etsu; Satonaka Hiroshi; Oba Shigeyoshi; Nishimatsu Hiroaki; Omata Masao; Fujita Toshiro; Nagai Ryozo; Hirata Yasunobu

TI Blockade of endogenous cytokines mitigates neointimal formation in obese **Zucker rats**.

SO Circulation, (2005 Mar 22) 111 (11) 1398-406.
Journal code: 0147763. ISSN: 1524-4539.

AB BACKGROUND: It is well known that diabetes mellitus is a major risk factor for vascular diseases such as atherosclerosis and **restenosis** after angioplasty. It has become clear that advanced glycation end products (AGE) and their receptor (RAGE) are implicated in vascular diseases, especially in diabetes mellitus. Nevertheless, the mechanisms by which diabetes mellitus is often associated with vascular diseases remain unclear. METHODS AND RESULTS: To study the role of endogenous cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 in the development of vascular diseases and in the expression of RAGE, we used semapimod, a pharmacological inhibitor of cytokine production, and examined its effect on neointimal formation in the femoral artery of obese **Zucker** (OZ) **rats**. We also used an adenovirus construct expressing a dominant negative mutant of the receptor for TNF-alpha (AdTNFRDeltaC) to block the action of endogenous TNF-alpha. Semapimod significantly suppressed neointimal formation and RAGE expression in OZ rats compared with untreated OZ rats. This inhibitory effect of semapimod on neointimal formation was overcome by infection of an adenovirus expressing RAGE into the femoral artery of OZ rats. Furthermore, AdTNFRDeltaC infection significantly suppressed neointimal formation and RAGE expression in the femoral artery of OZ rats. CONCLUSIONS: These results suggest that endogenous cytokines, especially TNF-alpha, were implicated in neointimal formation in OZ rats and that RAGE was a mediator of the effect of these cytokines on neointimal formation.

L6 ANSWER 4 OF 18 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AU Jonas M; Edelman E R; Groothuis A; Baker A B; Seifert P; Rogers C (Reprint)

TI Vascular neointimal formation and signaling pathway activation in response

to stent injury in insulin-resistant and diabetic animals

SO CIRCULATION RESEARCH, (30 SEP 2005) Vol. 97, No. 7, pp. 725-733. ISSN: 0009-7330.

AB Diabetes and insulin resistance are associated with increased disease risk and poor outcomes from cardiovascular interventions. Even drug-eluting stents exhibit reduced efficacy in patients with diabetes. We now report the first study of vascular response to stent injury in insulin-resistant and diabetic animal models. Endovascular stents were expanded in the aortae of obese insulin-resistant and type 2 diabetic **Zucker rats**, in streptozotocin-induced type 1 diabetic Sprague-Dawley rats, and in matched controls. Insulin-resistant rats developed thicker neointima (0.46 +/- 0.08 versus 0.37 +/- 0.06 mm(2), P=0.05), with decreased lumen area (2.95 +/- 0.26 versus 3.29 +/- 0.15 mm(2), P=0.03) 14 days after stenting compared with controls, but without increased vascular inflammation (ED1+ tissue macrophages). Insulin-resistant and diabetic rat vessels did exhibit markedly altered signaling pathway activation 1 and 2 weeks after stenting, with up to a 98% increase in p-ERK (anti-phospho ERK) and a 54% reduction in p-Akt (anti-phospho Akt) stained cells. Western blotting confirmed a profound effect of insulin resistance and diabetes on Akt and ERK signaling in stented segments. p-ERK/p-Akt ratio in stented segments uniquely correlated with neointimal response (R-2=0.888, P=0.04) in insulin-resistant and type 1 and 2 diabetic rats, but not in lean controls. Transfemoral aortic stenting in rats provides insight into vascular responses in insulin resistance and diabetes. Shifts in ERK and Akt signaling related to insulin resistance may reflect altered tissue repair in diabetes accompanied by a shift in metabolic: proliferative balance. These findings may help explain the increased vascular morbidity in diabetes and suggest specific therapies for patients with insulin resistance and diabetes.

L6 ANSWER 5 OF 18 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AU Barbato J E; Zuckerbraun B S; Overhaus M; Raman K G; Tzeng E (Reprint)

TI Nitric oxide modulates vascular inflammation and intimal hyperplasia in insulin resistance and the metabolic syndrome

SO AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (JUL 2005) Vol. 289, No. 1, pp. H228-H236. ISSN: 0363-6135.

AB Type 2 diabetes mellitus (DM) and the metabolic syndrome, both characterized by insulin resistance, are associated with an accelerated form of atherosclerotic vascular disease and poor outcomes following vascular interventions. These vascular effects are thought to stem from a heightened inflammatory environment and reduced bioavailability of nitric oxide (NO). To better understand this process, we characterized the vascular injury response in the obese **Zucker rat** by examining the expression of adhesion molecules, the recruitment of inflammatory cells, and the development of intimal hyperplasia. We also evaluated the ability of exogenous NO to inhibit the sequela of vascular injury in the metabolic syndrome. Obese and lean **Zucker rats** underwent carotid artery balloon injury. ICAM-1 and P-selectin expression were increased following injury in the obese animals compared with the lean rats. The obese rats also responded with increased macrophage infiltration of the vascular wall as well as increased neointima formation compared with their lean counterparts (intima/media = 0.91 vs. 0.52, P = 0.001). After adenovirus-mediated inducible NO synthase (iNOS) gene transfer, ICAM-1, P-selectin, inflammatory cell influx, and oxidized low-density lipoprotein (LDL) receptor expression were all markedly reduced versus injury alone. iNOS gene transfer also significantly inhibited proliferative activity (54% and 73%; P < 0.05) and neointima formation (53% and 67%; P < 0.05) in lean and obese animals, respectively. The vascular injury response in the face of obesity and the metabolic syndrome is associated with increased adhesion molecule

expression, inflammatory cell infiltration, oxidized LDL receptor expression, and proliferation. iNOS gene transfer is able to effectively inhibit this heightened injury response and reduce neointima formation in this proinflammatory environment.

L6 ANSWER 6 OF 18 MEDLINE on STN
AU Naka Yoshifumi; Bucciarelli Loredana G; Wendt Thoralf; Lee Larisse K; Rong Ling Ling; Ramasamy Ravichandran; Yan Shi Fang; Schmidt Ann Marie
TI RAGE axis: Animal models and novel insights into the vascular complications of diabetes.
SO Arteriosclerosis, thrombosis, and vascular biology, (2004 Aug) 24 (8) 1342-9. Electronic Publication: 2004-05-20. Ref: 58
Journal code: 9505803. ISSN: 1524-4636.
AB Receptor for AGE (RAGE) is a multi-ligand member of the immunoglobulin superfamily of cell surface molecules. Engagement of RAGE by its signal transduction ligands evokes inflammatory cell infiltration and activation in the vessel wall. In diabetes, when fueled by oxidant stress, hyperglycemia, and superimposed stresses such as hyperlipidemia or acute balloon/endothelial denuding arterial injury, the ligand-RAGE axis amplifies vascular stress and accelerates atherosclerosis and neointimal expansion. In this brief synopsis, we review the use of rodent models to test these concepts. Taken together, our findings support the premise that RAGE is an amplification step in vascular inflammation and acceleration of atherosclerosis. Future studies must rigorously test the potential impact of RAGE blockade in human subjects; such trials are on the horizon.

L6 ANSWER 7 OF 18 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
AU Grisk O (Reprint); Rettig R
TI Interactions between the sympathetic nervous system and the kidneys in arterial hypertension
SO CARDIOVASCULAR RESEARCH, (1 FEB 2004) Vol. 61, No. 2, pp. 238-246. ISSN: 0008-6363.
AB Elevated sympathetic activity changes renal function and accelerates the development of hypertension. Principles of sympatho-renal interactions in chronic hypertension are reviewed. Alterations in the ontogeny of the sympathetic nervous system and the kidney, inherited abnormalities in sensory receptor function and exaggerated responsiveness to mental stress contribute to inappropriately high sympathetic activity in primary or essential hypertension. Careful characterization of clinical study populations shows that elevated sympathetic activity and "essential" hypertension are not unequivocally associated. Prospective clinical studies which investigate a broader array of physiological functions and experiments in recombinant inbred rodents with less traumatic nerve recording techniques than currently available will help to define under which conditions elevated sympathetic activity is indeed a cause of primary hypertension. Signals arising from the kidney which activate the renin-angiotensin system and afferent renal nerves increase sympathetic activity. These mechanisms importantly contribute to the pathogenesis of hypertension secondary to renal artery **stenosis** and end-stage renal disease. (C) 2003 European Society of Cardiology. Published by Elsevier B.V.

L6 ANSWER 8 OF 18 MEDLINE on STN DUPLICATE 3
AU Stenina Olga I; Krukovets Irene; Wang Kai; Zhou Zhongmin; Forudi Farhad; Penn Marc S; Topol Eric J; Plow Edward F
TI Increased expression of thrombospondin-1 in vessel wall of diabetic **Zucker rat**.
SO Circulation, (2003 Jul 1) 107 (25) 3209-15. Electronic Publication: 2003-06-16.
Journal code: 0147763. ISSN: 1524-4539.
AB BACKGROUND: Thrombospondin-1 (TSP-1) expression in the vascular wall has

been related to the development of atherosclerotic lesions and **restenosis**. TSP-1 promotes the development of neointima and has recently been associated with atherogenesis at a genetic level. Because TSP-1 expression is responsive to glucose stimulation in mesangial cells, we hypothesized that glucose may stimulate its production by vascular cells. Thus, TSP-1 expression in the blood vessel wall may increase, providing a molecular link between diabetes and accelerated vascular lesion development. METHODS AND RESULTS: To determine whether the expression level of TSP-1 in vessel wall is increased in diabetes, aorta and carotid arteries of **Zucker rats** were used for immunostaining, Western blotting, and in situ RNA hybridization. A significant increase in TSP-1 expression was found in the adventitia of blood vessels from diabetic rats. Consistent with the well-known antiangiogenic effect of TSP-1, the number of vasa vasorum was reduced in aortas from diabetic rats. In cultured endothelial cells, vascular smooth muscle cells, and fibroblasts, TSP-1 expression increased in response to glucose stimulation (>30-fold). After balloon catheter injury to carotid arteries, expression of TSP-1 protein and mRNA was higher at all time points in the vessels of diabetic rats. CONCLUSIONS: Increased expression of TSP-1 in blood vessels in diabetes may represent a new link between diabetes, atherogenesis, and accelerated **restenosis**. This increase in TSP-1 production may be a direct response of vascular cells to glucose.

L6 ANSWER 9 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 4
AU Zhou, Zhongmin; Wang, Kai; Penn, Marc S.; Marso, Steven P.; Lauer, Michael A.; Forudi, Farhad; Zhou, Xiaorong; Qu, Wu; Lu, Yan; Stern, David M.; Schmidt, Ann Marie; Lincoff, A. Michael; Topol, Eric J. [Reprint Author]
TI Receptor for AGE (RAGE) mediates neointimal formation in response to arterial injury.
SO Circulation, (May 6 2003) Vol. 107, No. 17, pp. 2238-2243. print. ISSN: 0009-7322 (ISSN print).
AB Background: Receptor for advanced-glycation end products (RAGE) and its ligands AGEs and S100/calgranulins have been implicated in a range of disorders. However, the role of RAGE/ligand interaction in neointimal hyperplasia after vascular injury remains unclear. Methods and Results: We examined the expression of RAGE and its ligands after balloon injury of the carotid artery in both **Zucker** diabetic and nondiabetic **rats**. Using a soluble portion of the extracellular domain of RAGE, we determined the effects of suppressing RAGE/ligand interaction on vascular smooth muscle cell (VSMC) proliferation and neointimal formation after arterial injury. We demonstrate a significantly increased accumulation of AGE and immunoreactivities of RAGE and S100/calgranulins in response to balloon injury in diabetic compared with nondiabetic rats. Blockade of RAGE/ligand interaction significantly decreased S100-stimulated VSMC proliferation in vitro and bromodeoxyuridine (BrdU)-labeled proliferating VSMC in vivo, and suppressed neointimal formation and increased luminal area in both **Zucker** diabetic and nondiabetic **rats**. Conclusions: These findings indicate that RAGE/ligand interaction plays a key role in neointimal formation after vascular injury irrespective of diabetes status and suggest a novel target to minimize neointimal hyperplasia.

L6 ANSWER 10 OF 18 MEDLINE on STN DUPLICATE 5
AU Shelton J; Wang D; Gupta H; Wyss J M; Oparil S; White C R
TI The neointimal response to endovascular injury is increased in obese **Zucker rats**.
SO Diabetes, obesity & metabolism, (2003 Nov) 5 (6) 415-23. Journal code: 100883645. ISSN: 1462-8902.
AB BACKGROUND: **Restenosis** after revascularization procedures is accelerated in persons with type 2 diabetes. AIM: The current study tested the hypothesis that the neointimal response to endovascular injury

is enhanced in female obese **Zucker** (OZ) **rats**, a model of type 2 diabetes. METHODS: Animals were randomized to receive either a standard diet (SD) or a diabetogenic diet (DD) for 6 weeks. Four weeks later, balloon injury of the right common carotid artery was induced. All rats were euthanized 2 weeks after injury. Lean **Zucker** (LZ) **rats** served as controls. RESULTS: At the time of death, plasma glucose was elevated in OZ rats fed a SD (208 +/- 13 mg/dl) and a DD (288 +/- 21 mg/dl) compared to corresponding LZ rats (SD: 153 +/- 8; DD: 132 +/- 7 mg/dl). The ratio of high-density lipoprotein cholesterol (HDLc) to total cholesterol (Totc), an index of atherogenicity, was reduced in OZ rats on both diets (SD: 0.77 +/- 0.06; DD: 0.80 +/- 0.09) compared to LZ controls (SD: 1.11 +/- 0.02; DD: 1.20 +/- 0.05). Histomorphometric analysis of injured arteries showed that the intima to media (I : M) ratio was significantly increased in OZ (1.37 +/- 0.07) compared to LZ (0.79 +/- 0.08) rats. Elevations in plasma glucose and triglycerides (Tg) correlated positively and decreases in HDLc negatively with an increased I : M ratio. Administration of the DD did not further enhance the I : M ratio in LZ (0.87 +/- 0.06) or OZ (1.29 +/- 0.09) rats. CONCLUSIONS: These results suggest that neointima formation following endoluminal injury of the carotid artery is enhanced at an early stage in the development of diabetes mellitus.

L6 ANSWER 11 OF 18 MEDLINE on STN DUPLICATE 6

AU Desouza Cyrus V; Murthy S N; Diez Jose; Dunne Bruce; Matta Anil S; Fonseca Vivian A; McNamara Dennis B

TI Differential effects of peroxisome proliferator activator receptor-alpha and gamma ligands on intimal hyperplasia after balloon catheter-induced vascular injury in **Zucker rats**.

SO Journal of cardiovascular pharmacology and therapeutics, (2003 Dec) 8 (4) 297-305.
Journal code: 9602617. ISSN: 1074-2484.

AB BACKGROUND: Patients with type 2 diabetes mellitus have a higher rate of **restenosis** following angioplasty. Peroxisome proliferator activator receptor-alpha (PPAR) and gamma ligands such as fenofibrate and rosiglitazone, respectively, have been shown to have protective effects on the vessel wall. We studied the effect of fenofibrate and rosiglitazone on intimal hyperplasia in the **Zucker rat**, a model for insulin resistance and type 2 diabetes mellitus, following balloon catheter-induced injury. METHODS AND RESULTS: Three groups of 13-week-old female fatty **Zucker rats** were administered an aqueous suspension of either 3 mg/kg/d rosiglitazone (n=7) or 150 mg/kg/d fenofibrate (n=6) by gavage, or served as controls (n=9). In addition, two groups of 13-week-old female lean **Zucker rats** were either administered 3 mg/kg/d rosiglitazone (n=6) or served as controls (n=6). Carotid balloon injury was induced 1 week after the drugs were started. The drug administration was continued for 3 weeks. A 2-mm balloon catheter was introduced through the femoral artery to the left carotid. The balloon was inflated to 4 atmospheres for 20 seconds and then was deflated to 2 atmospheres and dragged down to the aorta. The rats were killed 3 weeks after the injury. The carotid intima/media ratio was calculated. Intimal hyperplasia after carotid balloon-induced injury in the fatty **Zucker rats** was significantly reduced in the group treated with rosiglitazone (0.18 +/- 0.29) compared with the untreated group (0.97 +/- 0.13; P<.01). Plasma glucose, triglyceride, and insulin levels were elevated, indicative of the presence of insulin resistance; rosiglitazone treatment significantly reduced insulin and triglyceride levels without decreasing glucose. Rosiglitazone treatment also reduced, but to a lesser extent, the intimal hyperplasia in the lean **Zucker rats** (0.57 +/- 0.10 vs 1.06 +/- 0.12 treated and untreated, respectively; P<.01); however, it had no effect on insulin, triglyceride, or glucose levels in this group. The intimal hyperplasia in the fatty **Zucker rats** treated with fenofibrate was not reduced compared with controls (0.84 +/- 0.26 vs 0.97 +/- 0.13,

respectively); fenofibrate reduced insulin and triglyceride, but not glucose levels, in these animals. CONCLUSIONS: The PPAR-gamma ligand rosiglitazone, but not the PPAR-alpha ligand fenofibrate, decreases intimal hyperplasia following balloon injury in both fatty and lean **Zucker rats**. This effect of the PPAR-gamma ligand was independent of glycemia, insulin, and lipid levels, and was more pronounced in insulin-resistant rats.

L6 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
IN Stern, David M.; Schmidt, Ann-Marie; Marso, Steven; Topol, Eric; Lincoff, A. Michael
TI A method for inhibiting new tissue growth in blood vessels in a patient subjected to blood vessel injury
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002030889	A2	20020418	WO 2001-US32036	20011012
WO 2002030889	A3	20020711		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002013192	A5	20020422	AU 2002-13192	20011012

AB This invention provides for a method for inhibiting new tissue growth in blood vessels in a subject, wherein the subject experienced blood vessels injury, which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to inhibit new tissue growth in the subject's blood vessels. The invention also provides for method for inhibiting neointimal formation in blood vessels in a subject, wherein the subject experienced blood vessel injury, which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to inhibit neointimal formation in the subject's blood vessels. The invention also provides a method for preventing exaggerated **restenosis** in a diabetic subject which comprises administering to the subject a pharmaceutically effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) so as to prevent exaggerated **restenosis** in the subject. In the example provided, a significant reduction in neointimal area was observed in fatty **Zucker rats** treated with soluble receptor for advanced glycation endproduct following carotid artery injury.

L6 ANSWER 13 OF 18 MEDLINE on STN DUPLICATE 7
AU Zhou Zhongmin; Penn Marc S; Forudi Farhad; Zhou Xiaorong; Tarakji Khaldoun; Topol Eric J; Lincoff A Michael; Wang Kai
TI Administration of recombinant P-selectin glycoprotein ligand Fc fusion protein suppresses inflammation and neointimal formation in **Zucker** diabetic **rat** model.
SO Arteriosclerosis, thrombosis, and vascular biology, (2002 Oct 1) 22 (10) 1598-603.
Journal code: 9505803. ISSN: 1524-4636.
AB OBJECTIVE: P-selectin-mediated leukocyte-endothelium and leukocyte-platelet interaction has been reported after vascular injury and has been correlated with neointimal hyperplasia, but its role in neointimal formation after arterial injury in diabetes has not been described. METHODS AND RESULTS: Using a **Zucker** diabetic **rat** balloon injury model, we examined the role of P-selectin in

the vascular inflammatory process and neointimal formation after balloon injury. Immunohistochemistry revealed that P-selectin was intensely expressed and that CD45-positive leukocyte infiltration was significantly increased after arterial injury. A single preprocedural intravenous administration of a recombinant P-selectin-soluble glycoprotein ligand-Ig inhibited CD45-positive leukocyte accumulation and suppressed neointimal formation in the **Zucker** diabetic **rat** model.
CONCLUSIONS: These results suggest that reduction of P-selectin-mediated leukocyte activation with the use of recombinant P-selectin-soluble glycoprotein ligand-Ig decreases the inflammatory response and limits neointimal formation after balloon injury in diabetes.

L6 ANSWER 14 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AU Shelton, Jonathan [Reprint author]; Wang, Dajun [Reprint author]; Oparil, Suzanne [Reprint author]; White, C. Roger [Reprint author]
TI Effects of lipid lowering therapy on the vascular response to injury in a model of type 2 diabetes.
SO FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A1206-A1207. print. Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002. CODEN: FAJOEC. ISSN: 0892-6638.
AB Diabetes increases risk for **restenosis** following revascularization procedures. To study mechanisms underlying this response, balloon injury of the carotid artery was performed in diabetic obese **Zucker** (OZ) **rats** at 14 weeks of age. Lean **Zucker** (LZ) **rats** served as controls. Two weeks post injury, plasma glucose, insulin, and LDL were elevated in OZ rats compared to LZ controls. The damaged carotid was excised and processed for histomorphological analysis. The vascular response to injury was increased in OZ rats, as reflected by a greater intima to media (I-M) ratio compared to LZ controls (1.28+-0.10 v 0.72+-0.12). The increased I-M ratio in OZ rats was positively associated with elevated plasma LDL, LZ and OZ rats were randomized to receive either the lipid lowering agent lovastatin or the insulin sensitizing drug pioglitazone for 4 weeks prior to balloon injury. While lovastatin normalized plasma lipids, it did not affect I-M ratios in OZ or LZ rats. In contrast, pioglitazone reduced the I-M ratio in OZ rats (0.64+-0.12). These data suggest that hyperinsulinemia and/or insulin resistance, rather than dyslipidemia, are more important determinants of the neointimal response to injury in OZ rats.

L6 ANSWER 15 OF 18 MEDLINE on STN
AU Wendt Thoralf; Bucciarelli Loredana; Qu Wu; Lu Yan; Yan Shi Fang; Stern David M; Schmidt Ann Marie
TI Receptor for advanced glycation endproducts (RAGE) and vascular inflammation: insights into the pathogenesis of macrovascular complications in diabetes.
SO Current atherosclerosis reports, (2002 May) 4 (3) 228-37. Ref: 52 Journal code: 100897685. ISSN: 1523-3804.
AB The incidence and severity of atherosclerosis is increased in patients with diabetes. Indeed, accelerated macrovascular disease in diabetic patients has emerged as a leading cause of morbidity and mortality in the United States and worldwide. Multiple investigations have suggested that there are numerous potential contributory factors that underlie these observations. Our laboratory has focused on the contribution of receptor for advanced glycation endproducts (RAGE) and its proinflammatory ligands, advanced glycation endproducts (AGEs) and S100/calgranulins in vascular perturbation, manifested as enhanced atherogenesis or accelerated **restenosis** after angioplasty. In rodent models of diabetic complications, blockade of RAGE suppressed vascular hyperpermeability, accelerated atherosclerotic lesion area and complexity in diabetic apolipoprotein E-deficient mice, and prevented exaggerated neointimal

formation in hyperglycemic fatty **Zucker rats** subjected to injury of the carotid artery. In this review, we summarize these findings and provide an overview of distinct mechanisms that contribute to the development of accelerated diabetic macrovascular disease. Insights into therapeutic strategies to prevent or interrupt these processes are presented.

L6 ANSWER 16 OF 18 MEDLINE on STN DUPLICATE 8
AU Park S H; Marso S P; Zhou Z; Foroudi F; Topol E J; Lincoff A M
TI Neointimal hyperplasia after arterial injury is increased in a rat model of non-insulin-dependent diabetes mellitus.
SO Circulation, (2001 Aug 14) 104 (7) 815-9.
Journal code: 0147763. ISSN: 1524-4539.
AB BACKGROUND: The key biological determinants that promote **restenosis** in the setting of diabetes have not been elucidated. There is no accepted animal model to study **restenosis** in diabetes. METHODS AND RESULTS: We evaluated 2 models of diabetes mellitus: (1) streptozotocin (STZ)-treated Sprague-Dawley rats (type I diabetes) versus regular Sprague-Dawley **rats** and (2) obese **Zucker rats** (type II diabetes) versus lean **Zucker rats**. Neointimal hyperplasia was assessed after carotid balloon injury at 21 days by computerized morphometry. There was no difference in neointimal area in the STZ-treated rats compared with controls, irrespective of insulin administration or dose of STZ. Neointimal area was increased >2-fold in obese **Zucker rats** compared with lean **Zucker rats** (0.21+/-0.06 versus 0.08+/-0.03 mm(2), P<0.01). The neointimal area was markedly increased in the obese **Zucker rats** 7 days after injury (0.058+/-0.024 versus 0.033+/-0.009 mm(2), P<0.05) and persisted through 21 days. In both obese and lean **Zucker rats**, cell proliferation peaked in the media at 3 days (118.66+/-84.28 versus 27.50+/-12.75 bromodeoxyuridine-labeled cells per cross section). In the intima, cell proliferation markedly increased beginning at day 3 and persisted through day 14 in the obese and lean **Zucker rats** (202.27+/-98.86 versus 35.71+/-20.54 bromodeoxyuridine-labeled cells at 7 days). CONCLUSIONS: The type II diabetic rat model, typifying insulin resistance, is associated with a propensity for neointima. The obese **Zucker rat** model may be an ideal diabetic model to further characterize the diabetic vascular response to injury.

L6 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
IN Berge, Rolf
TI Use of non-β-oxidizable fatty acid analogs for treatment of Syndrome-X conditions
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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AB Pharmaceutical compns. for the treatment and/or prevention of the Syndrome-X conditions comprise non-β-oxidizable fatty acid analogs of the general formula alkyl-X-CH2COOR (alkyl = saturated or unsatd. C8-22; X = O, S, SO, SO2, Se; R = H, C1-4 alkyl). The compds. exhibit hypolipidemic, antidiabetic, antiobesity, antioxidant, and antihypertensive activities. E.g., tetradecylthioacetic acid (TDTAA) was suspended in 0.5% CM-cellulose and administered orally to male obese **Zucker** fa/fa **rats** at a dose of 300 mg/day/kg for 10 days. TDTAA exhibited a good hypolipidemic effect decreasing a lipid level in blood plasma by 72% (triglycerides), 73% (cholesterol), and 7% (phospholipids), compared with the control.

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AU EICH D M (Reprint); NESTLER J E; JOHNSON D E; DWORKIN G H; KO D; WECHSLER A S; HESS M L

TI INHIBITION OF ACCELERATED CORONARY ATHEROSCLEROSIS WITH DEHYDROEPIANDROSTERONE IN THE HETEROTOPIC RABBIT MODEL OF CARDIAC TRANSPLANTATION

SO CIRCULATION, (JAN 1993) Vol. 87, No. 1, pp. 261-269.
ISSN: 0009-7322.

AB Background. Accelerated coronary atherosclerosis has become a critical problem in cardiac transplantation. Although the pathogenesis of this disease is unknown, hypercholesterolemia has been shown to be a major risk factor.

Methods and Results. To study this problem, a hypercholesterolemic rabbit model of heterotopic cardiac transplantation was developed to study accelerated graft atherosclerosis. Based on suggestions in the literature, it was hypothesized that dehydroepiandrosterone (DHEA) may retard the progression of the disease. Using semiquantitative light microscopy, a predilection for the development of small vessel occlusive disease in the transplanted hearts was found. Chronic DHEA administration produced a 45% reduction in the number of significantly stenosed vessels in the transplanted hearts ($p<0.05$) compared with controls and a 62% reduction in the nontransplanted hearts ($p<0.05$), yielding an overall 50% reduction in the number of significantly stenosed vessels in both the transplanted and nontransplanted hearts. This reduction in luminal **stenosis** was observed in the absence of any significant alterations in lipid profiles.

Conclusions. It is concluded that chronic DHEA administration in a hypercholesterolemic rabbit model of heterotopic cardiac transplantation significantly retards the progression of accelerated atherosclerosis in both the transplanted heart and in the native heart.

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TI INHIBITION OF ACCELERATED CORONARY ATHEROSCLEROSIS WITH DEHYDROEPIANDROSTERONE IN THE HETEROTOPIC RABBIT MODEL OF CARDIAC TRANSPLANTATION
AU EICH D M (Reprint); NESTLER J E; JOHNSON D E; DWORKIN G H; KO D; WECHSLER A S; HESS M L
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background. Accelerated coronary atherosclerosis has become a critical **problem** in cardiac transplantation. Although the pathogenesis of this disease is unknown, hypercholesterolemia has been shown to be a major risk factor.

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Conclusions. It is concluded that chronic DHEA administration in a hypercholesterolemic rabbit model of heterotopic cardiac transplantation significantly retards the progression of accelerated atherosclerosis in both the transplanted heart and in the native heart.